Exercise in the heat is limited by a critical internal temperature

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Walters, T. J., K. L. Ryan, L. M. Tate, and P. A. Mason. Exercise in the heat is limited by a critical internal temperature. *J Appl Physiol* 89: 799–806, 2000.—We examined whether fatigue during exertional heat stress occurred at a critical internal temperature independent of the initial temperature at the start of exercise. Microwaves (2.1 GHz; 100 mW/cm^2) were used to rapidly (3–8 min) heat rats before treadmill exercise to exhaustion. In a repeated-measures design, food-restricted male Sprague-Dawley rats ($n = 11$) were preheated to three levels (low, medium, and high). In addition, two sham exposures, Sham 1 and Sham 2, were administered at the beginning and end of the study, respectively. At the initiation of exercise, hypothalamic (T_{hyp}) and rectal (T_{rec}) temperatures ranged from 39.0°C to 42.8°C (T_{hyp}) and 42.1°C (T_{rec}). The treadmill speed was 17 m/min (8° grade), and the ambient temperature during exercise was 35°C. Each treatment was separated by 3 wk. Run time to exhaustion was significantly reduced after preheating. There was a significant negative correlation between run time and initial T_{hyp} and T_{rec} ($r = 0.73$ and 0.74, respectively). The temperatures at exhaustion were not significantly different across treatments, with a range of 41.9–42.2°C (T_{hyp}) and 42.2–42.5°C (T_{rec}). There were no significant differences in run time in the sham runs administered at the start and end of the investigation. No rats died as a result of exposure to any of the treatments, and body weight the day after each treatment was unaffected. These results support the concept that a critical temperature exists that limits exercise in the heat.

brain; electromagnetic fields; hypothalamus; microwaves; thermoregulation; treadmill

ONE OUTCOME OF HYPERTHERMIA is a reduction in physical performance (9, 10). This has been observed in a wide variety of mammalian species, including various rodents (3, 5, 6), goats (2), various strains of antelope (20), the cheetah (21), dogs (24), and humans (6, 12, 14, 15). There is evidence that limitations in endurance performance in such situations may be due to the attainment of a critical internal temperature. In support of this hypothesis, direct thermal stimulation of the anterior hypothalamus results in reduced running performance in hamsters (8). Fuller et al. (5) have demonstrated that rats reach voluntary fatigue at the same hypothalamic temperature (T_{hyp}) and abdominal temperature despite differences in initial temperature. Recently, González-Alonso et al. (6) demonstrated that fatigue in trained athletes occurred at the same critical body and muscle temperature despite differences in initial internal temperature and its rate of rise. The manipulation of preexercise temperature is the most logical method of testing whether a critical temperature exists. However, such manipulation has been limited to a relatively narrow range. This is because the time required to increase baseline temperature using traditional heating modalities, i.e., environmental heating, can introduce confounding variables (e.g., dehydration) that are known to exert an influence on exercise.

The purpose of the present investigation was to test the hypothesis that a critical internal temperature limits exercise in the heat. This hypothesis was rigorously tested by manipulating preexercise temperatures over a heretofore-unexplored range of internal temperatures. This was accomplished by using microwave irradiation (MW) to rapidly heat rats before an exercise test involving a run to exhaustion in the heat. In addition, the repeated-measures design of the experiment allowed us to follow the health of the animal through the five experimental sessions; we were thus able to determine whether the temperature at which exhaustion occurred was below the level of gross thermal injury or lethality.

METHODS

Animals. Male Sprague-Dawley rats ($n = 11$) were obtained from the colonies of Charles River (Wilmington, MA). They were individually housed in standard plastic cages ($26 \times 23 \times 20.5$ cm) with water available ad libitum. Rats received Formulab 5008 (Purina Meals, St. Louis, MO) and were weighed twice a week. On receipt, all rats were maintained on a calorically restricted diet, receiving 60–63% of the diet consumed by rats fed ad libitum, as determined by a previous investigation (24). Food restriction was required to maintain all rats within the same weight range throughout

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the length of the investigation. Food was provided each day at 0500; any unconsumed food was removed at 0630. Removal of unconsumed food was not required after the first 3–4 days, because all rats learned to consume the ration within the allotted time interval. Rats were 4–5 mo old and weighed 380–390 g at the initiation of the experiment.

Stereotaxic surgery. Rats were anesthetized with a combination of ketamine (70 mg/kg ip), xylazine (10 mg/kg ip), and atropine (0.01 mg/kg ip) and placed on a thermostatically controlled water heating pad set to maintain a rectal temperature (T_{rec}) of 37°C. Rats then had a Vialon guide (Becton Dickinson) stereotaxically implanted into the hypothalamus. With the mouthpiece of the stereotaxic instrument set at -3.3, the coordinates for the tip of the guide were 1.8 mm posterior to bregma, 1.5 mm lateral from midline, and 8.3 mm below dura (17). The bottom of the guide was sealed, and the top of the guide was equipped with a threaded head cap. The cap was mated with a Tygon tether that contained the thermal probe used to measure T_{hyp} during experimentation. The guide was held in place with cranioplastic cement (Plastic One, Roanoke, VA) anchored to nylon screws.

Familiarization sessions. Before experimentation, rats were familiarized with restraint and treadmill (TM) running. Rats were first placed in a Styrofoam restrainer (22, 23) for 30 min. This was immediately followed by a 10-min period of TM running (model: Dual Economy, Columbus Instruments, Columbus, OH) at a speed of 13 m/min and a grade of 8°. Each rat received a minimum of four sessions spaced no less than 2 days apart. During each session, the tether was attached to the head cap, and the protective sleeve of the rectal probe was inserted 5 cm into the rectum and anchored to the tail with surgical tape. All sessions took place in the anechoic chamber used for the actual experiments, which was continuously maintained at 20–22°C.

Experimental procedure. Between 1200 and 1300 on the day of each experiment, a caged rat was transferred from the vivarium to the anechoic chamber. The rat was allowed to equilibrate for at least 1 h before initiation of the experiment. The rat was removed from the cage, fecal pellets were removed from the colon via gentle external massage, and the rat was weighed. To measure T_{rec}, a protective sleeve and thermistor (Vitek, model 101) were inserted 5 cm into the rectum and secured with surgical tape. The second thermistor, contained in a protective tether, was inserted into the guide cannula, and the tether was fastened to the head cap. The rat was then placed into the restrainer. Baseline temperatures were recorded, and the rat was treated with 2.06 GHz MW until the target T_{hyp} was reached. During sham treatments, rats were treated identically but were not irradiated. The duration of the sham treatments was 4 min and was based on the mean time required to reach $T_{hyp} = 41.5°C$ in MW-treated animals, as determined from previous experiments (22). The duration of MW ranged from 3.5 to 8.0 min, depending on the desired target temperature. Rats were observed during the exposures via closed-circuit camera and showed no sign of stress above that incurred during restraint alone. A more detailed description of the MW has been published previously (22, 23). During the 45- to 60-s period after MW, the rat was removed from the restrainer and was placed on the moving belt of the TM (18 m/min; 8° grade). The TM was enclosed, and the environmental temperature was maintained at 35° ± 1°C; this system has been previously described (23). The rat was then run until exhaustion was reached. Exhaustion was operationally defined as the point at which the rat would no longer run despite being pushed against the shock grid by the moving TM belt. An ohmmeter in series between the shocker and the grid provided confir-

mation that the rat was actually receiving electrical current. In addition, once the rat appeared to be unable to run, it was manually pushed to the front of the TM; in some cases rats would begin to run again after this procedure. Once exhaustion was confirmed, the rat was removed from the TM and was weighed, along with any fecal pellets collected during the run. The differences between the pre- and postrun body weights were recorded. No attempt was made to account for loss of body weight due to urination or salivation. During all experiments, rats were videotaped during the TM run. By use of a split screen, the digital display of the instruments was recorded on the same tape. All timing was done by using the stopwatch function on the video recorder.

Two experimenters were involved in each experiment. *Experimenter 1* was aware of the target condition and observed T_{hyp} during MW to determine when the target temperature had been reached and termination of MW was required. *Experimenter 2* stayed in another room, outside of the main room that housed the anechoic chamber. When MW was complete, *experimenter 2* was signaled to come in, he immediately entered the anechoic chamber, and the chamber door was closed. *Experimenter 2* then removed the rat from the restrainer and placed it on the moving TM belt. All instrumentation, video monitors, and timing devices were housed outside the anechoic chamber; thus *experimenter 2* had no cues regarding run duration or the internal temperatures of the rat during the experiment. Communication was one-way, via a microphone within the (soundproof) anechoic chamber to the audio channel of a video monitor outside the chamber. Thus *experimenter 1* could not communicate with *experimenter 2*. When *experimenter 2* had determined that exhaustion had occurred, *experimenter 2* told *experimenter 1*, who noted the duration of the run. Care was taken to ensure that *experimenter 2* remained blind to experimental conditions throughout the 13 wk of the investigation.

Treatments. In this repeated-measures investigation, rats were preheated using MW or were sham irradiated. The MW treatments entailed preheating the rats to the following target T_{hyp}: low (41.5°C); medium (42.5°C); and high (43.5°C), which were conducted in this order (Table 1). Because of concern that the most severe treatments might result in thermal injury or lethality, the treatments were presented in ascending level of severity rather than randomly. Sham trials were administered at the beginning (Sham 1) and end (Sham 2) of the investigation. Comparison of Sham 1 and Sham 2 allowed us to determine whether the rats had suffered any adverse effects as a result of the MW treatments. Thirteen weeks were required to complete all treatments; each treatment was separated by 3–4 wk (Table 1).

Microwave exposure. Rats were exposed for 3–8 min to 2.06-GHz radiation delivered in the far field at a power

Table 1. *Timetable of events*

Event	Weeks After Surgery
Surgery and recovery	0–2
Treadmill/restrainer familiarization	3–4
Sham 1	5
Low	8
Medium	12
High	15
Sham 2	18

In low, medium, and high treatments, rats were preheated by microwave irradiation to hypothalamic temperatures (T_{hyp}) of 41.5, 42.5, and 43.5°C, respectively. In sham treatments, rats were treated identically but were not irradiated.

Table 2. *Run time to exhaustion; T_{hyp} and T_{rec} following microwave preheating and at the start and end of exercise*

Treatment	Run Time, min	Preheat		Exercise Start		Exercise End	
		T_{hyp}, °C	T_{rec}, °C	T_{hyp}, °C	T_{rec}, °C	T_{hyp}, °C	T_{rec}, °C
Sham 1	38.1 ± 5.5	39.4 ± 0.1	39.5 ± 0.1	39.4 ± 0.1	39.5 ± 0.1	42.2 ± 0.2	42.4 ± 0.1
	(22.3–71.5)	(38.6–39.5)	(38.9–40.1)	(38.7–39.5)	(38.9–40.1)	(41.5–42.8)	(41.6–43.1)
Sham 2	35.8 ± 3.9	39.0 ± 0.2	39.0 ± 0.2	39.0 ± 0.2	39.0 ± 0.2	42.2 ± 0.2	42.5 ± 0.1
	(20.5–55.2)	(37.8–39.9)	(37.3–39.6)	(37.8–39.8)	(37.4–39.7)	(41.4–42.4)	(41.7–43.0)
Low	30.2 ± 4.2	41.5 ± 0.1	40.0 ± 0.3	40.8 ± 0.1	40.2 ± 0.3	41.9 ± 0.2	42.3 ± 0.1
	(17.4–61.1)	(41.4–41.5)	(40.0–40.7)	(40.5–41.0)	(40.0–40.9)	(40.9–42.5)	(41.7–42.7)
Medium	19.4 ± 3.0*	42.5 ± 0.1	41.1 ± 0.1	41.7 ± 0.1	41.2 ± 0.1	42.0 ± 0.1	42.2 ± 0.1
	(4.2–35.3)	(42.4–42.5)	(41.0–41.5)	(41.5–42.2)	(41.0–41.5)	(41.9–42.2)	(41.6–42.6)
High	7.1 ± 2.3*†‡	43.5 ± 0.1	42.1 ± 0.1	42.8 ± 0.1	42.1 ± 0.1	42.5 ± 0.1§	42.4 ± 0.1
	(0.5–20.4)	(43.4–43.6)	(41.6–42.8)	(42.5–43.5)	(41.7–42.8)	(41.9–43.5)	(41.6–42.8)

Values are means ± SE (range shown in parentheses); $n = 11$ rats. *Compared with Sham 1. †Compared with Sham 2. ‡Compared with low. §Compared with medium. All temperature values across treatments at preheat and start times were significantly different from each other. No comparisons between hypothalamic (T_{hyp}) and rectal temperature (T_{rec}) were made. $P < 0.05$ for all comparisons.

density of 100 mW/cm^2 in the keh-polarization (i.e., face toward the transmitter). The MW system has been previously described in detail (22, 23)

Statistical analysis. Using SigmaStat (Jandel; version 2.0) software, two-way ANOVA for repeated measures and Newman-Keuls post hoc tests were conducted on T_{hyp} and T_{rec} at baseline, immediately on termination of MW, at the initiation of exercise, and at the end of exercise. Time to exhaustion among treatments was compared by use of the same statistical method. When it became apparent that high treatment produced two subsets (runners and nonrunners; see DISCUSSION), unpaired *t*-tests were performed to determine significant differences between T_{hyp} and T_{rec} levels in these two subgroups. All data presented in RESULTS are means ± SE. Statistical significance was set at $P \leq 0.05$.

RESULTS

Influence of initial body temperature. The initial T_{hyp} and T_{rec} were significantly different among all treatments, including the two Sham trials (Table 2). Despite this fact, there was no significant difference in the T_{hyp} or T_{rec} at which exhaustion took place, with the exception of a significantly higher T_{hyp} at exhaustion after the high treatment. All animals stopped running at a T_{hyp} of 41.9–42.5°C and a T_{rec} of 42.2–42.5°C. Despite a separation of 13 wk, the temperatures at which exhaustion occurred after the two Sham treatments did not differ. Additionally, run time was significantly reduced in a dose-dependent fashion after MW treatments. Importantly, time to exhaustion did not differ between sham treatments.

During the high treatment, four rats were not able to run after preheating, although the remaining 7 rats ran. To further investigate this observation, we separated the rats able to run and those unable to run into two subgroups (runner and nonrunner, respectively), and separate statistical analyses were performed. Although all rats were heated to the identical T_{hyp} (43.5°C), the T_{rec} for the runners was significantly lower at the end of MW (Table 3). At the initiation of exercise, both the T_{hyp} and T_{rec} were significantly lower in the runners. It should be noted that, at the end of exercise, the T_{hyp} (42.2°C) and T_{rec} (42.3°C) for runners were not significantly different from the previous treatments. When the thermal profiles for high subgroups are plotted with all other treatments (Fig. 1), it can be seen that the T_{hyp} and T_{rec} at the time of fatigue were similar among all animals that ran.

Correlation between initial temperature and run time. There was a significant negative correlation between initial T_{hyp} and T_{rec} vs. time to exhaustion (Fig. 2, *A* and *B*). The *r* values were −0.73 and −0.74 for initial T_{hyp} vs. run time and T_{rec} vs. run time, respectively.

Thermal load. The thermal load during exercise was statistically similar for all treatments. The thermal loads (in °C · min above a T_{rec} of 40.0°C) for each treatment were as follows: Sham 1, 42.2 ± 4.3; Sham 2, 37.4 ± 5.3; low, 40.3 ± 6.0; medium, 43.8 ± 5.3; and high runners, 35.0 ± 5.2.

Table 3. *Run time to exhaustion*

Subgroup	Run Time, min	Preheat		Exercise Start		Exercise End	
		T_{hyp}, °C	T_{rec}, °C	T_{hyp}, °C	T_{rec}, °C	T_{hyp}, °C	T_{rec}, °C
Runner ($n = 7$)	10.7 ± 2.0	43.5 ± 0.1	41.9 ± 0.1*	42.6 ± 0.0*	41.9 ± 0.1*	42.2 ± 0.1	42.3 ± 0.1
	(3.6–20.4)	(43.4–43.5)	(41.4–42.2)	(42.5–42.7)	(41.5–42.2)	(41.9–42.4)	(41.6–42.6)
Nonrunner ($n = 4$)		43.5 ± 0.0	42.3 ± 0.1	43.0 ± 0.2	42.5 ± 0.1		
			(41.9–42.6)	(42.5–43.5)	(41.9–42.6)		

Values are means ± SE (range shown in parentheses). T_{hyp} and T_{rec} after microwave preheating and at the start and end of exercise with the High treatment were separated into subgroups on the basis of whether the rat could run (runner) or was unable to run (nonrunner) after microwave preheating. Because the nonrunner subgroup was unable to run, there are no postexercise (end) values. *Compared with nonrunner subgroup ($P < 0.05$).

Fig. 1. Hypothalamic (T_{hyp}; *top*) and rectal (T_{rec}; *bottom*) thermal profiles after microwave irradiation (MW) preheating and during exercise. *A*, MW-preheating (or sham) period, which lasted 3–8 min, depending on the target temperature desired; *B*, period required to transfer the rat from the restrainer to the treadmill (<1 min); *C*, exercise period. The final point for each treatment corresponds to the mean temperature at the mean run time for that treatment; mean error bars are SE of run time. The dashed line connects this point to the point corresponding to the mean temperature at the minimum run time for that treatment. See Tables 3 and 4 for results of the statistical analysis. In treatment groups without MW heating before (Sham 1) and after (Sham 2) heating treatments and with MW heating to T_{hyp} of 41.5 (low) and 42.5°C (medium), $n = 11$. With MW heating treatment to 43.5°C (high), $n = 7$ in subgroup of rats that ran (runner) and $n = 4$ in subgroup of rats that were unable to run (nonrunner).
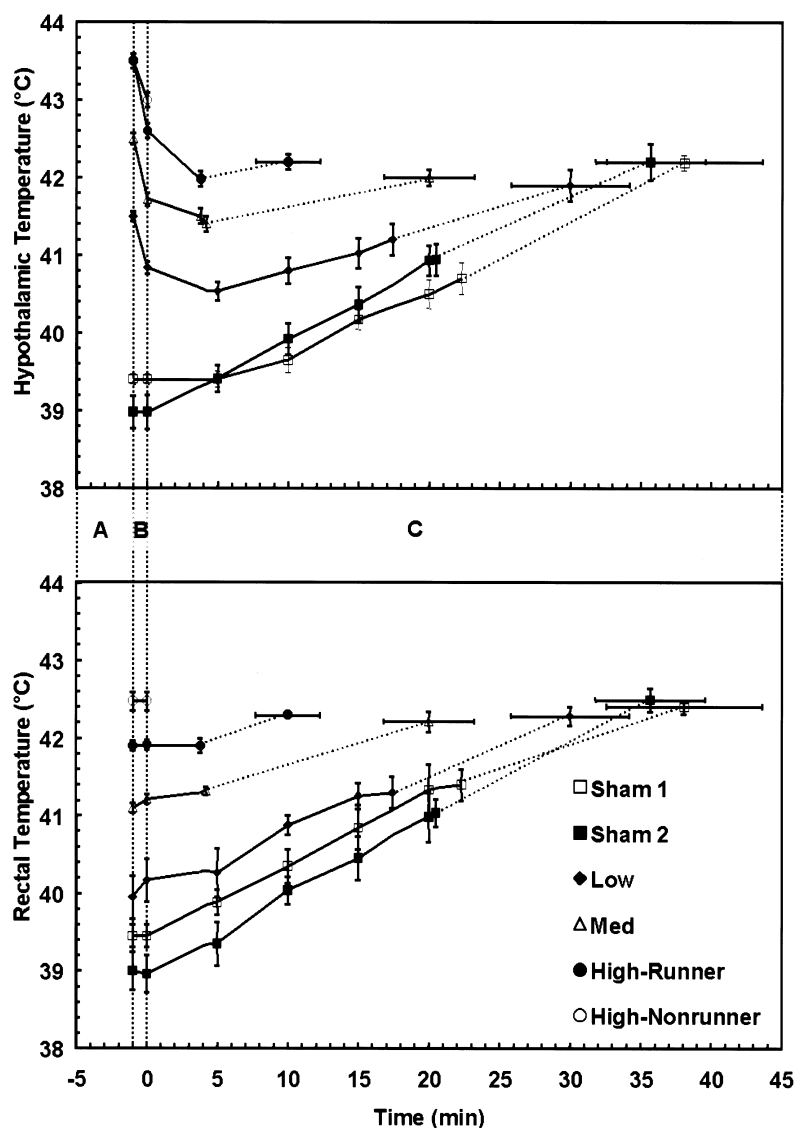
Animal status. During the 13 wk spanning the first treatment to the final treatment, the average increases in body weight were 10 g (Table 4). There was no immediate (1 day) or long-term (7 day) effect of the treatments on body weight. The magnitude of weight loss after each treatment is shown in Table 4. Sham 1, Sham 2, and low treatments resulted in significantly greater weight loss during exercise compared with medium and high treatments. Additionally, it should be noted that all animals survived each treatment.

DISCUSSION

The major finding of the present investigation was that, in exercising rats, exhaustion is reached at a T_{hyp} and T_{rec} of 42.1°C and 42.4°C, respectively, regardless of the temperatures at the initiation of exercise. This provides clear support for the concept that a critical internal temperature limits moderate exercise in the heat. There are a number of reports that have linked internal temperature to impaired physical perfor-

mance in the heat in humans and in animals. Caputa et al. (2) reported that reduced running performance occurred when T_{hyp} reached 42.0–42.9°C in exercising goats. Furthermore, cheetahs cease running when their core temperature reaches 40.5°C (21), whereas domestic dogs (beagles) reach exhaustion at T_{rec} between 41.7 and 42.2°C (24). Endurance-trained humans exercising in the heat become exhausted at between 39.7 and 40.3°C (6, 15). These studies have primarily used two different strategies to examine the question of whether a critical, exercise-limiting internal temperature exists. The first method is by altering the rate of heating during exercise by varying ambient temperature during exercise (6, 12, 24). The second method, and the one used in the present investigation, involves the use of heating (5, 6) or cooling (6, 14) before exercise to alter the initial temperature. When environmental heating is used as a preheating modality, the number of levels of preheating is limited. This is because the length of time required to induce a
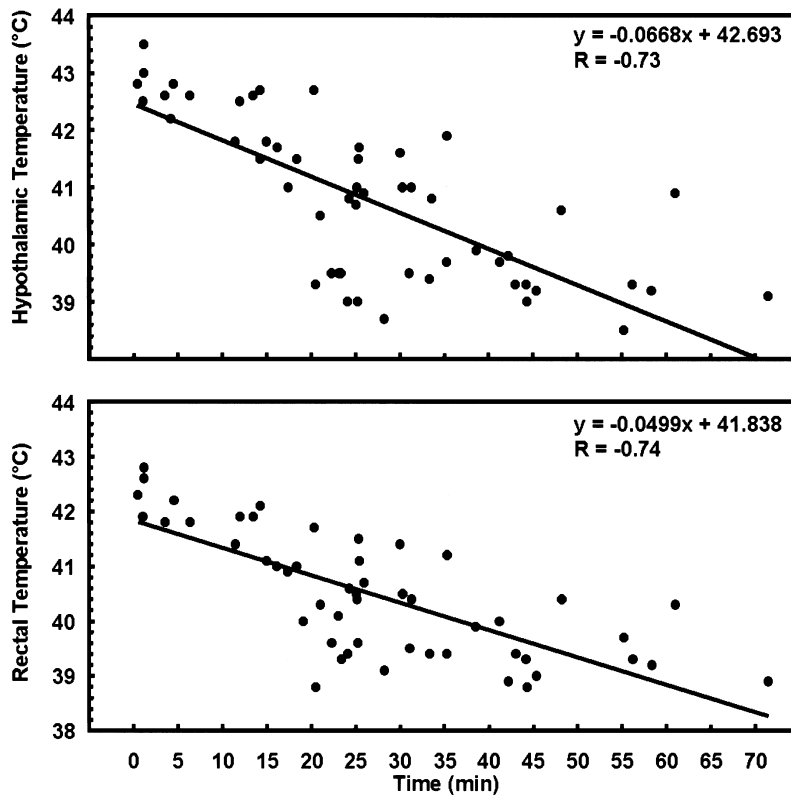
Fig. 2. Scatterplots of the initial (start of exercise) T_{hyp} (*top*) and T_{rec} (*bottom*) vs. time to exhaustion. Equations for regression lines and correlation coefficients are shown. In both cases, there was a significant negative correlation ($P < 0.05$).

significant elevation in baseline temperature eventually leads to the introduction of confounding variables such as dehydration, electrolyte imbalances, and cardiovascular drift that hasten fatigue during exercise. Using MW, we were able to preheat animals over a very wide range of preexercise levels in a very brief period of time (3–8 min), thereby avoiding these problems. It should be noted, however, that very brief MW exposures at this level might result in alterations in the cardiovascular system and/or cardiovascular regulation that might affect these results. The cardiovascular response to such MW exposures has not been determined to date.

As noted in METHODS, the treatments were presented from low to high. On the basis of our hypothesis, we expected that, after the high treatment, rats would be

unable to run, because exercise would be initiated above the threshold temperature at which they had stopped running in the previous treatments. However, this was not the case for all of the rats. Although four rats were unable to run, seven rats were able to run for a short period of time. In an attempt to explain this observation, the data from this treatment were divided into two subsets, runners and nonrunners, and the thermal data were analyzed separately (Table 3; Fig. 1). The results of the statistical analysis revealed a significant difference in the T_{rec} at the end of MW (Table 3). This occurred despite the attainment of identical T_{hyp}. At the initiation of exercise, the runners had T_{rec} below 41.9°C, which is below the mean temperatures displayed at exhaustion after the other treatments. The T_{hyp} of the runners, although not below the threshold temperature at the start of exercise, rapidly fell below it during the first few minutes of exercise (Fig. 1). Both temperatures then rose to 42.2–42.3°C, at which point exhaustion was reached. Thus we effectively bracketed the critical temperature with the runners and nonrunners of the high treatment. This treatment alone provides compelling evidence for the existence of a temperature that limits physical performance in the heat.

There are two aspects of MW heating that must be appreciated to understand the present investigation. First, at a frequency of 2.06 GHz, the heating in the head is greater than that in the trunk (22). Thus, when MW is terminated, the relatively cooler blood of the trunk perfuses the head, resulting in a precipitous drop in temperature. This is best illustrated in Fig. 1, in

Table 4. *Magnitude of weight loss at the end of each treatment and body weight immediately before, 1 day after, and 7 days after treatment*

		Body Weight, g		
Treatment	Weight Loss, g	Before Treatment	1 day after Treatment	7 days after Treatment
Sham 1	5.9 ± 0.8	367 ± 2	369 ± 3	366 ± 2
Sham 2	4.9 ± 0.8	377 ± 2	378 ± 3	372 ± 3
Low	4.6 ± 0.8	367 ± 3	370 ± 4	372 ± 4
Medium	3.6 ± 0.7*†‡	373 ± 2	371 ± 2	374 ± 2
High	3.0 ± 0.4*†‡	375 ± 2*	377 ± 2	371 ± 1

Values are means ± SE; n = 11 rats. *Compared with Sham 1; †Compared with Sham 2; ‡Compared with low ($P < 0.05$).

which it can be seen that T_{hyp} drops $\sim 0.7°C$ in the 1-min period between the termination of MW and the initiation of exercise, reflecting a mixing with the cooler blood of the trunk. At the same time, there is a slight increase in the T_{rec}, reflecting mixing with the warmer blood of the head. This is why the T_{hyp} for low, medium, and high treatments were higher immediately after MW compared with the initiation of exercise. Second, the orientation of the head relative to the MW emitter has a dramatic influence on brain heating (22). When the head is pointing directly toward the emitter, optimal heating takes place in the brain. When the head is turned 90° to the side, brain heating is dramatically reduced. This concept is important in the explanation of why the thermal profiles of the runners and nonrunners occurred after the high treatment. Our animal restrainers used a guillotine-type head catch; although the animal's body is fixed, its head is free to rotate 90° to the side. If the rat turns its head in this fashion, energy deposition in the brain is significantly less efficient, requiring longer to reach the same T_{hyp} (22). The longer exposure period allows the core (T_{rec}) to increase more. Conversely, when the rat's head is facing the emitter, the MW period is shorter, and T_{rec} increases less for the same increase in T_{hyp}. This is why the runners had a significantly lower T_{rec} compared with the nonrunners at the end of MW. The lower T_{rec} (reflective of a relatively cooler trunk) in the runners in turn caused a significantly greater decline in T_{hyp} at the initiation of exercise when compared with that of the nonrunners.

A recent investigation in rats demonstrated that voluntary fatigue occurs at a T_{hyp} of 40.1–40.2°C regardless of temperature at the initiation of exercise (5). These temperatures were much lower than those reported herein. The main difference between our investigations is the end point examined. Fuller et al. (5) used voluntary fatigue as their end point, whereas rats in our investigation were motivated by a classic shock-avoidance paradigm. As pointed out by these investigators (5), it is difficult to assess fatigue in animal studies involving the thermal limits of exercise. In their investigation, no source of coercion was used to force rats to run. Fatigue was defined as "the point at which the rat was unable to keep pace with the treadmill and lay flat on, and rode, the belt for a period of 3 minutes" (5). This describes the postural extension response, a well-documented thermoregulatory behavior displayed by rats as well as a number of other animals [for review, see Gordon (9)]. The response allows the animal *1*) to increase the body surface area's contact with a cooler surface, thus facilitating conductive heat transfer, and *2*) to reduce metabolic heat production via muscle relaxation (18). Although this is an important thermoregulatory behavior, we do not believe that this represents an analogous level of fatigue to that observed in highly motivated human subjects. It was clear from previous work that, when coerced, rats easily run at body temperatures above the temperature at which the postural extensor response is observed. We believe that fatigue, defined as the inability to avoid shock, represents a level of motivation that is closer to that observed in highly motivated endurance athletes or military personnel. Although this is a more rigorous end point than that used by Fuller et al. (5), the rats in our study were not forced to run to the point that they were unable to right themselves when placed on their backs, which is a traditional definition of exhaustion in rat exercise studies (4, 11, 19). At the point of fatigue, rats were still able to walk on the TM at a reduced speed.

It has been proposed that a critical sublethal temperature exists beyond which physical activity is not possible; such a mechanism is hypothesized to protect the animal from reaching a lethal level of hyperthermia (2, 9, 21). It is noteworthy that there were no fatalities after any of the treatments in the present investigation. Indirect indexes of the health of our animals are the maintenance of body weight after each treatment (Table 4) and the similar run times and temperature at exhaustion for Sham 1 compared with Sham 2 (Table 3; Fig. 1). These gross observations indirectly suggest that the animals ceased exercise before suffering thermal injury. Histopathology studies are currently underway to explore this hypothesis more fully.

Studies designed to assess lethality of exertional heat stress have demonstrated that rats will run to the point of heatstroke leading to death (4, 11, 19). However, it must be emphasized that it is not the temperature alone that determines the lethality of heat stress, but rather the thermal load, which is determined by the level of hyperthermia and the duration for which it is sustained (4, 11). We calculated the thermal load encountered by our rats during exercise by the method of Fruth and Gisolfi (4) and found similar values (37.4–43.8°C · min) after all treatments. This range of values is below the lethal thermal load reported for untrained rats by Fruth and Gisolfi. Thus our rats became fatigued before they reached a lethal thermal load. In the present study, as well as in a previous investigation (23), we found that rats always became too fatigued to run before lethal thermal loads were encountered. Studies that have exercised rats to lethality have intentionally designed the exercise protocol to maximize the thermal load encountered by the animals. This has been accomplished by either running rats under a work-rest paradigm at a low level of exercise (11, 19) or by ramping up exercise intensity and environmental temperature during the course of the session (4). Interestingly, in this last study (4), fatigue occurred at a T_{rec} (42.4°C) similar to the one we report. In contrast to our study, however, Fruth and Gisolfi reported 100% mortality. The difference between the studies relates to the thermal load. Although exhaustion was reached at the same temperature in both studies, Fruth and Gisolfi used ramped-up temperature and TM speed to produce a thermal load threefold greater than that achieved in our investigation. This is important because it suggests that, although there may be a critical temperature beyond which exercise cannot continue in the heat, it is not sensitive to thermal load and thus cannot protect

against thermal damage or lethality under all circumstances. Another condition in which the critical temperature cannot protect against lethality can occur during low-level exercise in the heat. Under these conditions, a lethal thermal load can occur before the critical temperature for cessation of exercise is reached (11, 19).

Although this investigation provides evidence for the existence of a limiting body temperature during exercise in the heat, it is not clear how these limits are controlled. Exercise ceased at a similar T_{hyp} and T_{rec} independent of the level of preheating; thus it cannot be determined from the present study whether fatigue is related to elevated brain or core temperature. It was not possible to measure metabolic indicators associated with fatigue (e.g., blood glucose, lactate, or muscle glycogen concentrations) because of the repeated-measures design of the study. If these factors were involved, however, it is unlikely that their influence would coincide with the same internal temperatures across treatments. In addition, exercise after medium and high was only 19.4 and 10.7 min, respectively, which is too short a time period in which to expect significant substrate depletion. Furthermore, it has been demonstrated in humans exercising in the heat that exhaustion occurs before significant decline in muscle glycogen and blood glucose concentrations or increases in muscle and blood lactate concentrations (14, 15, 16). A recent investigation in humans (16) has linked accumulation of IMP and NH_3 with fatigue in the heat. Studies in racehorses have led to the postulation that fatigue in the heat may also be due to metabolic dysfunction precipitated by oxidative stress (13). Although we cannot rule out these possibilities in the present investigation, they appear unlikely because of the fact that fatigue occurred at nearly the identical temperature after all treatments. Dehydration was also not a factor, given that the amount of weight lost during exercise does not reflect a level of dehydration associated with fatigue (Table 4).

It has been suggested that fatigue during exercise in the heat is related to a diminished central drive (1). The hypothalamus has been shown to be involved in a myriad of themoregulatory responses and behaviors [for review, see Gordon, Ref. (9)]. It would thus appear to be a likely candidate for limiting exercise in the heat. Caputa et al. (2) used intravascular heat exchangers to selectively heat and cool the brain and trunk independently in exercising goats. The results of these experiments have demonstrated that exhaustion is reached when T_{hyp} reaches 42.0–42.9°C if trunk temperature is maintained at 40.0°C. In contrast, a trunk temperature of over 43.5°C was required before exercise performance was affected. This suggests central involvement in mediating fatigue. The postural extension response, used by Fuller et al. (5) as their operational definition of fatigue, has been clearly demonstrated to occur in response to warming of the preoptic area of the anterior hypothalamus (18). Thus fatigue during volitional exercise in rats is most likely controlled by the hypothalamus. However, it is not clear whether the hypothalamus mediates fatigue under the more stringent criteria used in the present study. Although this study provides strong evidence for the existence of a critical temperature that limits exercise in the heat, additional investigations are required to determine where the locus of control resides. In addition, it remains to be determined whether temperature per se is the critical variable or whether the temperature just coincides with the limiting variable.

In summary, this study clearly demonstrates that exhaustion during exercise in the heat in rats occurs at a critical internal temperature level regardless of the initial levels of temperature. By using MW technology, we were able to set initial temperature at various levels rapidly, thereby avoiding confounding factors inherent to more familiar modalities of pre-exercise heating. Because the temperatures at exhaustion were virtually identical, whereas the run times to exhaustion were correlated with the initial temperatures, this study provides strong evidence that exercise is limited by the attainment of a critical internal temperature.

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